REMARKS

Claims 9-13 were pending in the present application and were rejected. Claims 9-12 are herein amended. Claim 13 is herein cancelled without prejudice.

Applicants' Response to Claim Objections

The Office Action objects to claims 9-13 because claim 9 recites the phrase "a gene *of* an osteo-/chondro-inducible transcription factor Cbfa1." The Office Action states that this does not conform to the generally accepted scientific terms, since a gene refers to nucleic acid sequences that encode a protein, which encompasses a transcription factor Cbfa1.

In response, Applicants first respectfully clarify that pending claim 9 recites "a gene of an osteo-inducible transcription factor Cbfal." It does not recite an osteo-/chondro-inducible transcription factor. It appears that the Office Action has combined the language of original claim 1, and pending claim 9. Applicants respectfully request that future Office Actions take care to address the pending claims as written, not the original, cancelled claims, or a combination of the original and pending claims. However, in response to the objection, Applicants herein amend claim 9 to recite "a gene encoding an osteo-inducible transcription factor Cbfal." Favorable reconsideration is respectfully requested.

Applicants' Response to Claim Rejections under 35 U.S.C. §102

Claim 9 was rejected under 35 U.S.C. §102(b) as being anticipated by Yang et al. ("In Vitro and In Vivo Synergistic Interactions Between the Runx2/Cbfa1 Transcription

Factor and Bone Morphogenic Protein-2 in Stimulating Osteoblast Differentiation," ***Journal of Bone and Mineral Research*****, Vol. 18(4), p. 705-15, 2003).**

Yang is directed at a study of bone morphogenic proteins, growth factors and transcription factors. "Cbfa1" is also known as "Runx2." The studied genes were inserted into adenoviruses, and the adenoviruses transduced into the cells. Then, "[t]o measure in vivo osteogenic activity, virally transduced cells were subcutaneously implanted into immunodeficient mice." Abstract, lines 11-12. Thus, the transduced cells were directly implanted into the subject mice.

In response, Applicants respectfully submit that Yang does not disclose or suggest the invention as claimed. Specifically, claim 9 is directed at an implant consisting of a bioadaptable porous material. The bioadaptable porous materials in the present invention acts as a scaffold which enables the sustained release of the Cbfa1 gene at the defective site. This results in remarkable osteogenesis (bone formation).

On the other hand, Yang describes that interactions of various factors are needed for osteogenesis. In Yang, cells transduced with AdCMV-Runx2 (an adenoviral vector carrying a gene encoding Cbfa1) strongly express osteoblast markers such as ALP. The cells of Yang are subcutaneously implanted into immunodeficient mice. In Yang, the cells transduced with AdCMV-Runx2(Cbfa1) are implanted into mice without using a scaffold such as bioadaptable porous material. Accordingly, Applicants respectfully submit that Yang does not disclose or suggest the invention as claimed. Favorable reconsideration is respectfully requested.

Claims 9-13 were rejected under 35 U.S.C. §102(a) and under 35 U.S.C. §102(e) as being anticipated by Kumta et al. (U.S. Patent Application Publication No. 2003/0219466).

It is the position of the Office Action that Kumta discloses the invention as claimed. Kumta is directed at a method of manufacturing hydroxyapatite and uses therefore in delivery of nucleic acids. Kumta is primarily directed at the manufacturing of hydroxyapatite. However, Kumta also discusses complexing hydroxyapatite with a biomaterial. As discussed in paragraph [0022], "the biomaterial is plasmid DNA that contains a gene, such as a bone morphogenic protein gene." Kumta also identifies rhBMP-2, Osx, Runx2 (also known as Cbfa1), PDGF, NGF, VEGF, IGF, FDFs, EGF, TGF-β, and BMP-7.

Kumta describes a use of hydroxyapatite in delivery of a nucleic acid. Kumta teaches that hydroxyapatite can be conjugated with a biomaterial such as plasmid DNA containing a gene encoding a humoral factor such as BMP, Cbfa1, etc. The plasmid DNA is incorporated into a hydroxyapatite nanoparticle at the time of synthesizing the nanoparticle using $CaCl_2$ and Na_3PO_4. See paragraph [0101]. Kumta also describes that an adenovirus can be used as a vector for the delivery. The biomimetic extracellular matrix such a fibrinogen is adsorbed on the surface of the particle, but the plasmid DNA is conjugated in the particle. See paragraph [0118], claims 19-29 and the Examples.

In the method of the present invention, an adenoviral vector carrying a gene encoding Cbfa1 is adsorbed on a bioadaptable porous material. However, Kumta does not adsorb the vector on a bioadaptable porous material. Rather, in Kumta, an adenoviral vector is conjugated in the hydroxyapatite nano particle. Thus, the present invention enables *in situ* sustained release

of Cbfa1 gene and achieves remarkable bone regeneration. This is clearly demonstrated in the Examples of the present invention.

The conjugate of Kumta needs a large amount of adenoviral vector to synthesize the hydroxyapatite conjugate, because the adenoviral vector should be incorporated into the hydroxyapatite during the synthesis process of the hydroxyapatite conjugate. In contrast, the implant of the present invention is produced using a smaller amount of adenoviral vector via adsorption by the porous body.

In addition, the hydroxyapatite nano particle of Kumta cannot be sintered and has lower strength. Meanwhile, the bioadaptable porous material of the present invention can be sintered to enhance its strength. Also, the bioadaptable porous material used in the present invention shows higher cell infiltration and angioinvasive properties, while the hydroxyapatite nano particle used in Kumta shows no such properties.

With respect to claims 10-12 reciting of β-TCP, the Office Action refers to paragraph [0086], which discloses that hydroxyapatite decomposes into β-TCP and CaO. However, it appears that this decomposition into β-TCP and CaO is only performed in the context of analysis of the hydroxyapatite manufacturing process. There does not appear to be any suggestion or disclosure of a β-TCP bioadaptable porous material comprising an adenovirus carrying a gene encoding Cbfa1. Favorable reconsideration is respectfully requested.

Claims 9-13 were rejected under 35 U.S.C. §102(a) and under 35 U.S.C. §102(e) as being anticipated by Doll et al. (U.S. Patent Application Publication No. 2003/0235564).

It is the position of the Office Action that Doll discloses the invention as claimed. Doll is directed at compositions and devices comprising the Runx2 protein. Doll discloses using either the Runx2 protein itself, a polynucleotide encoding the Runx2 protein, or a cell that has been transformed with a polynucleotide encoding the Runx2 protein. Paragraph [0010]. Doll discloses the use of retroviral and adenoviral vectors at paragraph [0096]-[0098]. The Office Action states that paragraph [0053] discloses the use of β-TCP. Although paragraph [0053] does not appear to disclose this, paragraphs [0052], [0055], [0056], and [0086] appear to disclose the use of tricalcium phosphates.

In response, Applicants respectfully submit that while Doll describes the use of some elements of the invention, it does not disclose or suggest the specific constitution of the present invention. That is, Doll does not disclose or suggest "an implant consisting of a bioadaptable porous material on which an adenoviral or retroviral vector carrying a gene encoding an osteo-inducible transcription factor Cbfa1 is adsorbed." Doll does not disclose or suggest such an implant. Favorable reconsideration is respectfully requested.

For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

Should the Examiner deem that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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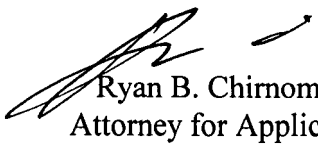

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